

REMARKS

It has come to our attention that an error is found in the relaxin-3 b-chain amino acid sequence represented by SEQ ID NO:3 in the Substitute Sequence Listing submitted June 14, 2006. A "Ser" residue at position 25 has inadvertently been omitted from this sequence. The enclosed second Substitute Sequence Listing corrects this omission by insertion of the missing "Ser at position 25 of SEQ ID NO:3.

Support for this correction may be found in prior art publicly available as of the June 20, 2003 priority date, copies of which are enclosed for the convenience of the Examiner. Relevant pages from PCT published application WO 03/030930 contain reference to relaxin H3 B chain as SEQ ID NO:2 on page 4, lines 10-16; page 5, lines 4-10; pages 5, line 31, through page 6, line 6; page 16, lines 1-7; page 17, lines 19-25; page 19, lines 1-5; page 20, lines 1-7; Fig. 1A, "B Chain"; Fig. 2A, "B Chain Aligns", "Human 3"; and "SEQUENCE LISTING", page 1/6, "H3-B chain", SEQ ID NO:2, where the "Ser" residue at position 25 is present.

In addition, copies of GenBank Accession No. Q8WXF3 and the corresponding entries from the UniProt/Swiss-Prot database showing sequence submission before the June 20, 2003 priority date are included. The GenBank entry also describes the region of the relaxin 3 preproprotein from amino acid positions 26-52 as "processed active peptide" and the "FEATURE" section of the UniProtKB Entry Q8WXF3 includes a "PEPTIDE" described as "Relaxin-3 B chain", each with the "Ser" at position 25 in agreement with the amino acid sequence of the corrected version of SEQ ID NO:3.

This amendment is accompanied by a floppy disk containing the above named sequences, SEQ ID NOS:1-25, in computer readable form, and a paper copy of the sequence information that has been printed from the floppy disk.

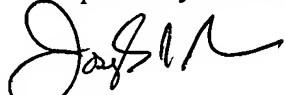
The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy. This amendment contains no new matter.

Appl. No. 10/561,304
Amdt. dated March 19, 2007
Reply to Notification of Missing Requirements of March 16, 2006
Supplemental Preliminary Amendment

PATENT

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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WO 03/030930 A1

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Desmond [AU/AU]; 1A Milton Street, Canterbury, Victoria 3126 (AU).

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(74) Agents: **STEARNE, Peter, Andrew et al.**; Davies Collison Cave, Level 10, 10 Barrack Street, Sydney, New South Wales 2000 (AU).

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(30) Priority Data:
PR 8144 8 October 2001 (08.10.2001) AU

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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WO 03/030930 A1

(54) Title: **HUMAN 3 RELAXIN**

(57) Abstract: Human H3 preprorelaxin, human H3 prorelaxin, human H3 relaxin, human relaxin analogues having a modified A chain and/or a modified B chain are described. Also described are nucleic acid sequences encoded human H3 preprorelaxin, human H3 prorelaxin, human H3 relaxin, human relaxin analogues. Also described are methods for the treatment of conditions responsive to administration of H3 relaxin or analogues thereof.

- 4 -

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser
1 5 10 15

5 Lys Ser Glu Ile Ser Ser Leu Cys
20

(SEQ ID NO: 4)

or an amino acid sequence truncated by up to about 9 amino acids from N-terminus,

10 the B chain having the amino sequence:

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
1 5 10 15

15 Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp
20 25

(SEQ ID NO: 2)

or an amino acid sequence truncated by up to 9 amino acids from the amino-terminus
and/or up to about 5 amino acids from the carboxyl-terminus,

20 the A and B chains being linked by interchain disulphide bonds at A11-B10, and A24-B22,
and wherein the human H3 relaxin or analogue thereof has relaxin bioactivity.

25 In a third aspect of the invention there is provided a composition comprising a human H3
relaxin analogue having a modified A chain and/or a modified B chain,

the H3 relaxin A chain having the amino acid sequence:

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser
30 1 5 10 15

Lys Ser Glu Ile Ser Ser Leu Cys

20

(SEQ ID NO: 4)

- 5 -

wherein the carboxyl-terminus is an amide derivative and/or Lys at position 12 is replaced with Glu, and/or Glu at position 19 is replaced with Gln,

the H3 relaxin B chain having the amino acid sequence:

5

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg

1 5 10 15

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp

10

20 25

(SEQ ID NO: 2)

wherein the carboxyl-terminus is an amide derivative, and/or Ala at position 2 is replaced with Pro, and/or Arg at position 8 is replaced with Lys,

15 the A and B chains being linked by disulphide bonds between A11-B10 and A24-B22 and wherein the human H3 relaxin analogue has relaxin bioactivity.

In accordance with a fourth aspect of the invention there is provided a composition comprising human H3 preprorelaxin or human H3 prorelaxin, having a signal, A chain, B chain and C chain in respect of human H3 preprorelaxin, and an A chain, B chain and C chain in respect of human H3 prorelaxin, the said amino acid chains having the amino acid sequences:

the A chain comprising:

25

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser

1 5 10 15

Lys Ser Glu Ile Ser Ser Leu Cys

30

20

(SEQ ID NO: 4)

the B chain comprising:

- 6 -

Arg Ala' Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
1 5 10 15

5 Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp
20 25 (SEQ ID NO: 2)

the signal sequence comprising:

10 Met Ala Arg Tyr Met Leu Leu Leu Leu Ala Val Trp Val Leu Thr
1 5 10 15

Gly Glu Leu Trp Pro Gly Ala Glu Ala
20 25 (SEQ ID NO: 1)

15

and the C chain comprising:

Arg Arg Ser Asp Ile Leu Ala His Glu Ala Met Gly Asp Thr Phe Pro
1 5 10 15

20

Asp Ala Asp Ala Asp Glu Asp Ser Leu Ala Gly Glu Leu Asp Glu Ala
20 25 30

25

Met Gly Ser Ser Glu Trp Leu Ala Leu Thr Lys Ser Pro Gln Ala Phe
35 40 45

Tyr Arg Gly Arg Pro Ser Trp Gln Gly Thr Pro Gly Val Leu Arg Gly
50 55 60

30 Ser Arg

65 (SEQ ID NO: 3)

In accordance with a fifth aspect of the invention there is provided a composition comprising the C chain of human H3 relaxin, the C chain having the amino acid sequence:

- 16 -

B Chain

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
1 5 10 15

5

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp

20

25

(SEQ ID NO: 2)

the A and B chains being linked by disulphide bonds between A11-B10, A24-B22.

10

Human H3 relaxin possesses classical relaxin bioactivity. Human relaxins, H1 and H2 relaxin, bind to cells expressing relaxin receptors, such as THP-1 cells (Parsell et al (1996) *J. Biol. Chem.* 271, 27936-27941). H2 relaxin produces a dose dependent increase in cAMP production from these cells. Synthetic H3 relaxin produced according to this invention stimulated a dose dependent increase in cAMP in keeping with human H2 relaxin. The specificity of response in target cells bearing the human relaxin receptor as exhibited by H3 relaxin is demonstrated by the inability of bovine insulin (bINSL) or human insulin (hINSL3) to stimulate cAMP responses at doses up to 1 um in THP-1 cells.

20

The elicitation of a second messenger response (cAMP) by stimulating human relaxin receptors with human H3 relaxin, provides definitive evidence that human H3 relaxin has classic relaxin biological activity. Such assays in cells containing relaxin receptors, for example THP-1 cells as referred to above provides, a ready way to determine relaxin activity. In addition, the ability of human H3 relaxin to compete with P³²-labelled H2 relaxin in binding to relaxin binding sites in cells expressing relaxin receptors, again provides definitive confirmation of relaxin activity.

25

Other biological activities/assays for determining relaxin activity are known in the art. For example, bioassays used for the measurement of active relaxin during pregnancy and non-pregnancy, such as the guinea pig interpubic ligament assay may be used (Steinert et al (1960) *Endocrinology* 67, 102-115, and Sirosi et al (1983) *American Journal of Obstetrics and Gynaecology* 145: 402-405) may be used. Other bioassays include cAMP production

30

- 17 -

in THP-1 cells (Parsell *et al* (1996) J. Biol. Chem 271, 27936-27941).

Applicant has found that H3 relaxin analogues may be prepared where up to 9 amino acids are truncated from the N-terminus of the A chain, and up to 9 amino acids are truncated
5 from the N-terminus of the B chain, and up to 5 amino acids are truncated from the C-terminus of the B chain.

The resulting relaxin analogues comprise a H3 relaxin A and B chain, the A chain having the amino acid sequence

10

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser
1 5 10 15

Lys Ser Glu Ile Ser Ser Leu Cys

15

20

(SEQ ID NO: 4)

truncated by up to about 9 amino acids from amino-terminus,

and the B chain having the amino acid sequence:

20

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
1 5 10 15

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp

25

20

25

(SEQ ID NO: 2)

truncated by up to 9 amino acids from the amino-terminus and/or up to about 5 amino acids from the carboxyl-terminus,

30 the A and B chains being linked by disulphide bonds between A11-B10 and A24-B22, and wherein the human H3 relaxin or analogue thereof has relaxin bioactivity. The A chain of human H3 relaxin contains an intrachain disulphide bond between Cys residues 10 and 15.

- 19 -

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
1 5 10 15

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp

5 20 25 (SEQ ID NO: 2)

wherein the carboxyl-terminus is an amide derivative, and/or Ala at position 2 is replaced with Pro, and/or Arg at position 8 is replaced with Lys,

- 10 the A and B chains being linked by disulphide bonds between A11-B10 and A24-B22, and wherein the human H3 relaxin analogue has relaxin bioactivity.

The isolation, purification and characterisation of nucleic acid sequences encoding human H3 relaxin has allowed the characterisation and production of the signal sequence of 15 human H3 relaxin, and the pro-sequence of human H3 relaxin.

The identification, purification and characterisation of the signal sequence and C chain of human H3 relaxin enables the prepro- and pro-human H3 relaxin to be produced.

- 20 In accordance with another aspect of the invention there is provided a composition comprising human H3 preprorelaxin or human H3 prorelaxin, having a signal, A chain, B chain and C chain in respect of human H3 preprorelaxin, and an A chain, B chain and C chain in respect of human H3 prorelaxin, the said amino acid chains having the amino acid sequences:

25

the A chain comprising:

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser
1 5 10 15

30

Lys Ser Glu Ile Ser Ser Leu Cys

20

(SEQ ID NO: 4)

- 20 -

the B chain comprising:

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
1 5 10 15

5

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp

20 25

(SEQ ID NO: 2)

the signal sequence comprising:

10

Met Ala Arg Tyr Met Leu Leu Leu Leu Leu Ala Val Trp Val Val Leu Thr
1 5 10 15

Gly Glu Leu Trp Pro Gly Ala Glu Ala

15

(SEQ ID NO: 1)

and the C chain comprising:

Arg Arg Ser Asp Ile Leu Ala His Glu Ala Met Gly Asp Thr Phe Pro
1 5 10 15

Asp Ala Asp Ala Asp Glu Asp Ser Leu Ala Gly'Glu Leu Asp Glu Ala
20 25 30

25

Met Gly Ser Ser Glu Trp Leu Ala Leu Thr Lys Ser Pro Gln Ala Phe
35 40 45

30

Ser Arg

65 (SEQ ID NO: 3)

In accordance with a further aspect of the invention there is provided the C chain of human H3 relaxin, said C chain having the amino acid sequence:

Fig. 1A

A: H3 relaxin assembled gene sequence

TATAAATGGGGGCCAAGAGGCAGCAGAGACACTGGCCCACTCTCACGTTCAAAGCGTCT

CCGTCCAGCATGGCCAGGTACATGCTGCTGCTCCCTGGCGGTATGGGTGCTGACCGGG****

M A R Y M L L L L A V W V L T G
Signal peptide

GAGCTGTGGCCGGGAGCTGAGGCCCGGGCAGCGCCTAACGGGTCAAGGCTTGCGGCCGA

E L W P G A E A R A A P Y G V R L C G R

GAATTCACTCCGAGCAGTCATCTCACCTGCGGGGCTCCCGGTGGAGACGATCAGACATC

E F I R A V I F T C G G S R W R R S D I
B Chain

CTGGCCCACGAGGCTATGG>>gtgaggctggggagagagatggatgtagaaggggaacag-

L A H E A M

-----intron 2318bp-----

-cactaactctgttcatctttgcag<<**GAGATAACCTCCCGATGCAGATGCTGATGAA**

G D T F P D A D A D E

GACAGTCTGGCAGGCCAGCTGGATGAGGCCATGGGTCCAGCGAGTGGCTGGCCCTGACC

D S L A G E L D E A M G S S E W L A L T
C Chain

AAGTCACCCAGGCCTTTACAGGGGGCACCCAGCTGGCAAGGAACCCCTGGGTTCTT

K S P Q A F Y R G R P S W Q G T P G V L

CGGGGCAGCCGAGATGTCTGGCTGGCCTTCAGCAGCTGCTGCAAGTGGGGTGTAGC

R G S R D V L A G L S S S C C K W G C S
A Chain

AAAAGTGAATCAGTAGCCTTGCTAGTTGAGGGCTGGCAGCCGTGGCACCAAGGACC

K S E I S S L C *
A Chain

AATGCCCAAGTCCTGCCATCCACTCAACTAGTGTCTGGCTGGCACCTGTCTTCGAGCC

TCACACATTCAATTCAATTCAACTACAAGTCACAGAGGCAGCTGTGGCTCAGGCACAGTCTC

CCGACACCACTATCCAACCTGCCCTTGACCAGCCTATCATGACCCCTGGCCCTAAGG

AAGCTGTGCCCTGCTGGTCAAGTGGGACCCCCCATCTGACCCCTGACCTCTCCCC

AGCCCTAACCATGCGTTGCCCTACACACTCCACTGCCACAACGGTCCCTACTC

TACCTAGGCTGCCACACAGAGACCCCTGCCCTCCAGTCCAAACTGTGGCCATTGT

CCCCTGACCAGCTAAATCAAGCCTCTGTCTCAGTCCAGCCTTGCAAGCAGCTTCC

TGCCCTGCTTCCATCCCCTCTCCCTCAACTCCCTGCCAGAGTCCAAGGCTGTGGAC

CCCAGAGAAGGTGGCAGGTGGCCCCCTAGGAGAGCTCTGGGCACATTGAATCTCCA

AACTCCAATAATAAAATTCAAGACTTGGCAGAGAGTGTGTGTGTATGGTTG

Fig. 2A

A.

B Chain Aligns

| | 1 | 5 | 10 | 15 | 20 | 25 |
|------------|-------------------------------------|---|----|----|----|----|
| Human 1 | KWKDDVIKLCGRELVRAQIAICGMSTWS | | | | | |
| Human 2 | DSWMEEVIKLCGRELVRAQIAICGMSTWS | | | | | |
| Cons 1,2,3 |++LCGRE.+RA.I..CG.S.W. | | | | | |
| Human 3 | RAAPYGVRLCGREFIRAVIFTCGGSRW | | | | | |
| Cons 3 | R.APYGV+LCGREFIRAVIFTCGGSRW | | | | | |
| Mouse 3 | RPAPYGVKLCGREFIRAVIFTCGGSRW | | | | | |
| Cons Mouse |++CGRE+.R.+I..CG.S.. | | | | | |
| Mouse 1 | RVSEEWMDGFIRMCGRAYARELIKICGASVGRLAL | | | | | |

A Chain Aligns

| | 1 | 5 | 10 | 15 | 20 | |
|------------|----------------------------------|---|----|----|----|--|
| Human 1 | R PYVALFEKCCLIGCTKRS LAKYC | | | | | |
| Human 2 | QLYSALANKCCHVGCTKRS LARFC | | | | | |
| Cons 1,2,3 | ...+.L....CC..GC+K..++..C | | | | | |
| Human 3 | DVLAGLSSSCCKWGCSKSEISSLC | | | | | |
| Cons 3 | DVLAGLSSSCC+WGCSKS+ISSLC | | | | | |
| Rat 3 | DVLAGLSSSCCEWGCSKSQISSLC | | | | | |
| Mouse 3 | DVLAGLSSSCCEWGCSKSQISSLC | | | | | |
| Cons Mouse | +....+S..CC..GCS+..I..L-C | | | | | |
| Mouse 1 | ESGGGLMSQQCCHVGCSRRSIAKLYC | | | | | |

SEQUENCE LISTING

<110> Howard Florey Institute of Experimental Physiology
and Medicine

5 University of Melbourne

<120> H3 Relaxin

<130> 7640120/PAS

10

<160> 10

<170> PatentIn version 3.0

15 <210> 1

<211> 25

<212> PRT

<213> H3-signal

20 <400> 1

Met Ala Arg Tyr Met Leu Leu Leu Leu Ala Val Trp Val Leu Thr

1 5 10 15

Gly Glu Leu Trp Pro Gly Ala Glu Ala

20 25

25

<210> 2

<211> 27

<212> PRT

<213> H3-B chain

30

<400> 2

Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg

1 5 10 15

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp

35

20 25

<210> 3

NCBI Protein My NCBI [Sign In] [Regis]

PubMed Nucleotide Protein Genome Structure PMC Taxonomy OMIM Books

Search Protein for

Limits Preview/Index History Clipboard Details

Display GenPept Show 5 Send to

Range: from begin to end Features: CDD

1: Q8WXF3. Reports Relaxin-3 precurs...[gi:37999891]

BLink, Conserved Domains, Links

| | Comment | Features | Sequence |
|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|----------|
| LOCUS | Q8WXF3 142 aa linear PRI 20-FEB-2007 | | |
| DEFINITION | Relaxin-3 precursor (Prorelaxin H3) (Insulin-like peptide INSL7) (Insulin-like peptide 7) [Contains: Relaxin-3 B chain; Relaxin-3 A chain]. | | |
| ACCESSION | Q8WXF3 | | |
| VERSION | Q8WXF3 GI:37999891 | | |
| DBSOURCE | swissprot: locus REL3_HUMAN, accession <u>Q8WXF3</u> ; class: standard. | | |
| | extra accessions: Q6UXW5 | | |
| | created: Oct 10, 2003. | | |
| | sequence updated: Mar 1, 2002. | | |
| | annotation updated: Feb 20, 2007. | | |
| | xrefs: AF447451.1, AAL40345.1, AB076563.1, BAC53758.1, AY358181.1, AAQ88548.1, 2FHWA, 2FHWB | | |
| | xrefs (non-sequence databases): UniGene:Hs.352155, Ensembl:ENSG00000171136, KEGG:hsa:117579, HGNC:17135, MIM: 606855, ArrayExpress:Q8WXF3, GermOnline:ENSG00000171136, RZPD-ProtExp:T3225, InterPro:IPR004825, SMART:SM00078, PROSITE:PS00262 | | |
| KEYWORDS | 3D-structure; Cleavage on pair of basic residues; Direct protein sequencing; Hormone; Signal. | | |
| SOURCE | Homo sapiens (human) | | |
| ORGANISM | <u>Homo sapiens</u> Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo. | | |
| REFERENCE | 1 (residues 1 to 142) | | |
| AUTHORS | Holloway,J.L., Lok,S. and Jaspers,S.R. | | |
| TITLE | Direct Submission | | |
| JOURNAL | Submitted (??-NOV-2001) | | |
| REMARK | NUCLEOTIDE SEQUENCE [MRNA]. | | |
| REFERENCE | 2 (residues 1 to 142) | | |
| AUTHORS | Kizawa,H., Nishi,K., Ishibashi,Y., Harada,M., Asano,T., Ito,Y., Suzuki,N., Hinuma,S., Fujisawa,Y., Onda,H., Nishimura,O. and Fujino,M. | | |
| TITLE | Production of recombinant human relaxin 3 in AtT20 cells | | |
| JOURNAL | Regul. Pept. 113 (1-3), 79-84 (2003) | | |
| PUBMED | <u>12686464</u> | | |
| REMARK | NUCLEOTIDE SEQUENCE [MRNA], AND PROTEIN SEQUENCE OF 26-34 AND 119-127. | | |
| REFERENCE | 3 (residues 1 to 142) | | |
| AUTHORS | Clark,H.F., Gurney,A.L., Abaya,E., Baker,K., Baldwin,D., Brush,J., | | |

Chen,J., Chow,B., Chui,C., Crowley,C., Currell,B., Deuel,B., Dowd,P., Eaton,D., Foster,J., Grimaldi,C., Gu,Q., Hass,P.E., Heldens,S., Huang,A., Kim,H.S., Klimowski,L., Jin,Y., Johnson,S., Lee,J., Lewis,L., Liao,D., Mark,M., Robbie,E., Sanchez,C., Schoenfeld,J., Seshagiri,S., Simmons,L., Singh,J., Smith,V., Stinson,J., Vagts,A., Vandlen,R., Watanabe,C., Wieand,D., Woods,K., Xie,M.H., Yansura,D., Yi,S., Yu,G., Yuan,J., Zhang,M., Zhang,Z., Goddard,A., Wood,W.I., Godowski,P. and Gray,A.

TITLE The secreted protein discovery initiative (SPDI), a large-scale effort to identify novel human secreted and transmembrane proteins: a bioinformatics assessment

JOURNAL Genome Res. 13 (10), 2265-2270 (2003)

PUBMED [12975309](#)

REMARK NUCLEOTIDE SEQUENCE [LARGE SCALE mRNA].
Erratum: [Genome Res. 2003 Dec;13(12):2759]

REFERENCE 4 (residues 1 to 142)

AUTHORS Sudo,S., Kumagai,J., Nishi,S., Layfield,S., Ferraro,T., Bathgate,R.A. and Hsueh,A.J.

TITLE H3 relaxin is a specific ligand for LGR7 and activates the receptor by interacting with both the ectodomain and the exoloop 2

JOURNAL J. Biol. Chem. 278 (10), 7855-7862 (2003)

PUBMED [12506116](#)

REMARK INTERACTION WITH LGR7.

REFERENCE 5 (residues 1 to 142)

AUTHORS Liu,C., Eriste,E., Sutton,S., Chen,J., Roland,B., Kuei,C., Farmer,N., Jornvall,H., Sillard,R. and Lovenberg,T.W.

TITLE Identification of relaxin-3/INSL7 as an endogenous ligand for the orphan G-protein-coupled receptor GPCR135

JOURNAL J. Biol. Chem. 278 (50), 50754-50764 (2003)

PUBMED [14522968](#)

REMARK INTERACTION WITH GPCR135.

REFERENCE 6 (residues 1 to 142)

AUTHORS Liu,C., Chen,J., Sutton,S., Roland,B., Kuei,C., Farmer,N., Sillard,R. and Lovenberg,T.W.

TITLE Identification of relaxin-3/INSL7 as a ligand for GPCR142

JOURNAL J. Biol. Chem. 278 (50), 50765-50770 (2003)

PUBMED [14522967](#)

REMARK INTERACTION WITH GPCR142.

COMMENT [FUNCTION] May play a role in neuropeptide signaling processes.
Ligand for LGR7, relaxin-3 receptor-1 (GPCR135) and relaxin-3 receptor-2 (GPCR142).
[SUBUNIT] Heterodimer of a B chain and an A chain linked by two disulfide bonds.
[SUBCELLULAR LOCATION] Secreted protein.
[SIMILARITY] Belongs to the insulin family.

FEATURES Location/Qualifiers

source 1..142
/organism="Homo sapiens"
/db_xref="taxon:[9606](#)"

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/gene="RLN3"
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/product="Relaxin-3 precursor"

Region 1..25
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/locus_tag="UNQ6188/PRO20213"

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/FTId=PRO_0000016082."
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/region_name="Beta-strand region"
/experiment="experimental evidence, no additional details
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Region
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/locus_tag="UNQ6188/PRO20213"
/region_name="I1GF"
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family; insulin family of proteins; groups a number of
active peptides which are evolutionary related including
insulin, relaxin, insulin-like growth factors I and II,
mammalian Leydig cell-specific insulin-like peptide (gene
INSL3), and early placenta insulin-like peptide (ELIP)
(gene INSL4), insect prothoracotrophic hormone
(bombyxin), locust insulin-related peptide (LIRP),
molluscan insulin-related peptides 1 to 5 (MIP), and C;
cd00101"
/db_xref="CDD:58309"
Bond
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details recorded"
/note="Interchain (between B and A chains) (By
similarity)."
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/experiment="experimental evidence, no additional details
recorded"
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/region_name="Helical region"
/experiment="experimental evidence, no additional details
recorded"
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bond(47,142)
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similarity)."
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/FTId=PRO_0000016084."
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/experiment="experimental evidence, no additional details recorded"
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/gene="RLN3"
/locus_tag="UNQ6188/PRO20213"
/bond_type="disulfide"
/inference="non-experimental evidence, no additional details recorded"
/note="By similarity."
Region 131
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/locus_tag="UNQ6188/PRO20213"
/region_name="Hydrogen bonded turn"
/experiment="experimental evidence, no additional details recorded"
Region 135..139
/gene="RLN3"
/locus_tag="UNQ6188/PRO20213"
/region_name="Helical region"
/experiment="experimental evidence, no additional details recorded"
Region 140..141
/gene="RLN3"
/locus_tag="UNQ6188/PRO20213"
/region_name="Hydrogen bonded turn"
/experiment="experimental evidence, no additional details recorded"

ORIGIN

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61 eamgdtfpda dadedslage ldeamgssew laltkspqaf yrgrpswqgt pgvlrgsr dv
121 laglssscck wgcskseiss lc

//

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UniProtKB Entry

[PIR View](#)UniProtKB Entry: **Q8WXF3****ENTRY INFORMATION**

| | |
|------------------------------------------|---------------------------------|
| ENTRY NAME | REL3_HUMAN |
| ACCESSION NUMBERS | Q8WXF3; Q6UXW5 |
| Integrated into Swiss-Prot on | 2003-10-10 |
| Sequence was last modified on | 2002-03-01 (Sequence version 1) |
| Annotations were last modified on | 2007-02-20 (Entry version 47) |

NAME AND ORIGIN OF THE PROTEIN

| | |
|------------------------|---------------------------------------------------------------------------------------------------------------------------|
| PROTEIN NAME | Relaxin-3 precursor |
| Synonyms | Prorelaxin H3 Insulin-like peptide INSL7 Insulin-like peptide 7 |
| Contains | Relaxin-3 B chain Relaxin-3 A chain |
| GENE NAME | Name: RLN3 Synonym: INSL7; RXN3; ZINS4 ORF name: UNQ6188/PRO20213 |
| SOURCE ORGANISM | Homo sapiens |
| TAXONOMY ID | 9606 [NCBI, NEWT] |
| LINEAGE | Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; M Primates; Haplorrhini; Catarrhini; Hominidae; Homo |

REFERENCES

| | |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| [1] | Holloway JL; Lok S; Jaspers SR. Homo sapiens insulin homolog polypeptide. Submitted (NOV-2001) to EMBL/GenBank/DDBJ databases. <i>Position: NUCLEOTIDE SEQUENCE [MRNA].</i> |
| [2] | Kizawa H; Nishi K; Ishibashi Y; Harada M; Asano T; Ito Y et al. View Production of recombinant human relaxin 3 in AtT20 cells. 2003, <i>Regul. Pept.</i> , 113, 79-84. |

| | |
|-----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| | <p>Position: NUCLEOTIDE SEQUENCE [mRNA]; PROTEIN SEQUE^R PubMed: 12686464; Medline: 22573778.</p> |
| [3] | <p>Clark HF; Gurney AL; Abaya E; Baker K; Baldwin DT; Brush J et al. The secreted protein discovery initiative (SPDI), a large-scale effort to identify transmembrane proteins: a bioinformatics assessment. 2003, <i>Genome Res.</i>, 13, 2265-2270.</p> <p>Position: NUCLEOTIDE SEQUENCE [LARGE SCALE mRNA]. PubMed: 12975309; Medline: 22887296.</p> |
| [4] | <p>Sudo S; Kumagai J; Nishi S; Layfield S; Ferraro T; Bathgate RAD et al. H3 relaxin is a specific ligand for LGR7 and activates the receptor and the exoloop 2. 2003, <i>J. Biol. Chem.</i>, 278, 7855-7862.</p> <p>Position: INTERACTION WITH LGR7. PubMed: 12506116; Medline: 22499664.</p> |
| [5] | <p>Liu C; Eriste E; Sutton S; Chen J; Roland B; Kuei C et al. View all. Identification of relaxin-3/INSL7 as an endogenous ligand for the GPCR135. 2003, <i>J. Biol. Chem.</i>, 278, 50754-50764.</p> <p>Position: INTERACTION WITH GPCR135. PubMed: 14522968;</p> |
| [6] | <p>Liu C; Chen J; Sutton S; Roland B; Kuei C; Farmer N et al. View all. Identification of relaxin-3/INSL7 as a ligand for GPCR142. 2003, <i>J. Biol. Chem.</i>, 278, 50765-50770.</p> <p>Position: INTERACTION WITH GPCR142. PubMed: 14522967;</p> |

COMMENTS

| | |
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| FUNCTION | May play a role in neuropeptide signaling processes. Ligand for LGR7, relaxin-3 receptor-2 (GPCR142). |
| SUBUNIT | Heterodimer of a B chain and an A chain linked by two disulfide bonds. |
| SUBCELLULAR LOCATION | Secreted protein. |
| SIMILARITY | Belongs to the insulin family. |

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DATABASE CROSS-REFERENCES

| | |
|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| ARRAYEXPRESS | Q8WXF3. |
| EMBL | AF447451, AAL40345.1, mRNA. [GenBank, DDBJ] AB076563, BAC53758.1, mRNA. [GenBank, DDBJ] AY358181, AAQ88548.1, ALT_INIT, mRNA. [GenBank, DDBJ] |
| ENSEMBL | ENSG00000171136, Homo sapiens. |
| GERMONLINE | ENSG00000171136, Homo sapiens |
| HGNC | HGNC:17135, RLN3. |
| INTERPRO | IPR004825, Ins/IGF/relax. |

| | |
|---------------------|-------------------------------------------------------------------|
| KEGG | hsa:117579. |
| MIM | 606855,gene. |
| PDB | 2FHW,NMR,A=119-142, B=26-52. |
| PROSITE | PS00262,INSULIN,1. |
| RZPD_PROTEXP | T3225 |
| SMART | SM00078,IIIGF,1. |
| UNIGENE | Hs.352155 |
| UniRef | View cluster of proteins with at least 50% / 90% / 100% identity. |

KEYWORDS

3D-structure; Cleavage on pair of basic residues; Direct protein sequencing; Hormone; Signal

| FEATURES | |
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| Feature | Description |
| SIGNAL PEPTIDE | |
| PEPTIDE | Relaxin-3 B chain (By similarity). /FTId=PRO_00000 |
| PROPEPTIDE | Connecting peptide (BY SIMILARITY) /FTId=PRO_00000 |
| PEPTIDE | Relaxin-3 A chain (By similarity). /FTId=PRO_00000 |
| DISULFIDE BOND | Interchain (between B and A chains) (BY SIMILARITY) |
| DISULFIDE BOND | Interchain (between B and A chains) (BY SIMILARITY) |
| DISULFIDE BOND | BY SIMILARITY |
| STRAND | |
| TURN | |
| HELIX | |
| TURN | |
| HELIX | |
| TURN | |
| HELIX | |
| TURN | |

Feature sequence (Put the mouse on the feature above to see the sequence below):

RAAPYGVRLCGREFIRAVIFTCGGSRW

| SEQUENCE | |
|-------------------------|------------------|
| LENGTH | 142 aa |
| MOLECULAR WEIGHT | 15451 Da |
| CRC64 CHECKSUM | 23A3E095034B31E4 |

| SEQUENCE | MARYMLLLL AVWVLTGELW PGAEARAAPY GVRLCGREFI RAVIFTCGGS RWRRSDILAH EAMGDTFPDA DADEDSLAGE LDEAMGSSEW LALTSPQAF 1 YRGRPSWQGT PGVLRGSRDV LAGLSSSCCK WGCSKSEISS LC 1 |
|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|

ADDITIONAL INFORMATION FROM iProClass [Go to iProClass](#)

| | |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| GENE/GENOME | <ul style="list-style-type: none"> ► <i>Gene Name:</i> RLN3; relaxin 3 <i>Synonyms:</i> H3; RXN3; ZINS4; insl7 ; <i>Map Location:</i> 19p13.2 Entrez Gene: 117579 UniGene: Hs.352155 RefSeq: NM_080864.2 NP_543140.1 [Map Viewer] NCBI GI#: g27372865; g18254464; g37181470; g15984431; g174840; g119604794 |
| BIBLIOGRAPHY | <ul style="list-style-type: none"> ► View Bibliography Information ► Submit Bibliography <i>Annotated references:</i> PMID: 14522967; 14522968; 15465925; 15845619; 15956686; 159512506116 [UniProt/GeneRIF] <i>Other references:</i> PMID: 12477932; 11689565 |
| PIRSF FAMILY | PIRSF037063 relaxin 3/insulin-like peptide 5 precursors; PIRSF5003 |
| GENE ONTOLOGY | <p><i>Molecular Function</i></p> <p>GO:0005179: hormone activity [INTERPRO; evidence:IEA] [SPKW]</p> <p><i>Biological Process</i></p> <p>GO:0007582: physiological process [INTERPRO; evidence:IEA]</p> <p><i>Cellular Component</i></p> <p>GO:0005576: extracellular region [INTERPRO; evidence:IEA]</p> |
| PATHWAY | KEGG: Neuroactive ligand-receptor interaction [PATH:hsa04080]. |
| STRUCTURE | PDB: 2FHW:A(119-142); 2FHW:B(26-52) 2FHW: SCOP CATH FSSP MMDB PDBsum |

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for Q8WXF3

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UniProtKB/Swiss-Prot entry Q8WXF3

[\[Entry info\]](#) [\[Name and origin\]](#) [\[References\]](#) [\[Comments\]](#) [\[Cross-references\]](#)
[\[Keywords\]](#) [\[Features\]](#) [\[Sequence\]](#) [\[Tools\]](#)

Note: most headings are clickable, even if they don't appear as links. They link to the user manual or other documents.

Entry information

| | |
|-----------------------------------|--------------------------------------|
| Entry name | REL3_HUMAN |
| Primary accession number | Q8WXF3 |
| Secondary accession number | Q6UXW5 |
| Integrated into Swiss-Prot on | October 10, 2003 |
| Sequence was last modified on | March 1, 2002 (Sequence version 1) |
| Annotations were last modified on | February 20, 2007 (Entry version 47) |

Name and origin of the protein

| | |
|--------------|----------------------------|
| Protein name | Relaxin-3 [Precursor] |
| Synonyms | Prorelaxin H3 |
| | Insulin-like peptide INSL7 |
| | Insulin-like peptide 7 |

Contains

| | |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gene name | Name: RLN3 Synonyms: INSL7, RXN3, ZINS4 ORFNames: UNQ6188/PRO20213 |
| From | Homo sapiens (Human) [TaxID: 9606] |
| Taxonomy | Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo. |

References

[1] NUCLEOTIDE SEQUENCE [MRNA].

Holloway J.L., Lok S., Jaspers S.R.;
 "Homo sapiens insulin homolog polypeptide.";
 Submitted (NOV-2001) to the EMBL/GenBank/DDBJ databases.

[2] NUCLEOTIDE SEQUENCE [MRNA], AND PROTEIN SEQUENCE OF 26-34 AND 119-121

DOI=10.1016/S0167-0115(02)00304-X; PubMed=12686464 [NCBI, ExPASy, EBI, Israel, .

Kizawa H., Nishi K., Ishibashi Y., Harada M., Asano T., Ito Y., Suzuki N., Hinuma S., Fujis Y., Onda H., Nishimura O., Fujino M.;
 "Production of recombinant human relaxin 3 in AtT20 cells."; Regul. Pept. 113:79-84(2003).

[3] NUCLEOTIDE SEQUENCE [LARGE SCALE RNA].

DOI=10.1101/gr.1293003; PubMed=12975309 [NCBI, ExPASy, EBI, Israel, Japan]

Clark H.F., Gurney A.L., Abaya E., Baker K., Baldwin D.T., Brush J., Chen J., Chow B., Cl Crowley C., Currell B., Deuel B., Dowd P., Eaton D., Foster J.S., Grimaldi C., Gu Q., Hass Heldens S., Gray A.M.;

"The secreted protein discovery initiative (SPDI), a large-scale effort to identify novel human secreted and transmembrane proteins: a bioinformatics assessment."; Genome Res. 13:2265-2270(2003).

[4] INTERACTION WITH LGR7.

DOI=10.1074/jbc.M212457200; PubMed=12506116 [NCBI, ExPASy, EBI, Israel, Japan]

Sudo S., Kumagai J., Nishi S., Layfield S., Ferraro T., Bathgate R.A.D., Hsueh A.J.W.;

"H3 relaxin is a specific ligand for LGR7 and activates the receptor by interacting with both ectodomain and the exoloop 2.";

J. Biol. Chem. 278:7855-7862(2003).

[5] INTERACTION WITH GPCR135.

DOI=10.1074/jbc.M308995200; PubMed=14522968 [NCBI, ExPASy, EBI, Israel, Japan]

Liu C., Eriste E., Sutton S., Chen J., Roland B., Kuei C., Farmer N., Joernvall H., Sillard R Lovenberg T.W.;

"Identification of relaxin-3/INSL7 as an endogenous ligand for the orphan G-protein coupled receptor GPCR135.";

J. Biol. Chem. 278:50754-50764(2003).

[6] INTERACTION WITH GPCR142.

DOI=10.1074/jbc.M308996200; PubMed=14522967 [NCBI, ExPASy, EBI, Israel, Japan]

Liu C., Chen J., Sutton S., Roland B., Kuei C., Farmer N., Sillard R., Lovenberg T.W.;

"Identification of relaxin-3/INSL7 as a ligand for GPCR142.";

J. Biol. Chem. 278:50765-50770(2003).

Comments

- **FUNCTION:** May play a role in neuropeptide signaling processes. Ligand for LGR7, relaxin receptor-1 (GPCR135) and relaxin-3 receptor-2 (GPCR142).
- **SUBUNIT:** Heterodimer of a B chain and an A chain linked by two disulfide bonds.
- **SUBCELLULAR LOCATION:** Secreted protein.
- **SIMILARITY:** Belongs to the insulin family.

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Cross-references

Sequence databases

| | | |
|------|------------------------------------------|-----------------------------------------------|
| | AF447451; AAL40345.1; -; mRNA. | [EMBL / GenBank / DDBJ] [CoCodingSequence] |
| EMBL | AB076563; BAC53758.1; -; mRNA. | [EMBL / GenBank / DDBJ] [CoCodingSequence] |
| | AY358181; AAQ88548.1; ALT_INIT; mRNA. | [EMBL / GenBank / DDBJ] [CoCodingSequence] |

UniGene Hs.352155

3D structure databases

PDB 2FHW; NMR; A=119-142, B=26-52.[ExPASy / RCSB / EBI]

ModBase Q8WXF3.

Organism-specific gene databases

HGNC HGNC:17135; RLN3.

GeneCards RLN3.

GeneLynx RLN3; Homo sapiens.

GenAtlas RLN3.

MIM 606855; gene. [NCBI / EBI]

HOVERGEN [Family / Alignment / Tree]

Gene expression databases

CleanEx HGNC:17135; RLN3.

ArrayExpress Q8WXF3; -.

GermOnline ENSG00000171136; Homo sapiens.

Family and domain databases

InterPro IPR004825; Ins/IGF/relax.

Graphical view of domain structure.

SMART SM00078; IIGF; 1.

SMART graphical view of domain structure.

PROSITE PS00262; INSULIN; 1.

ProDom [Domain structure / List of seq. sharing at least 1 domain]

BLOCKS Q8WXF3.

Genome annotation databases

Ensembl ENSG00000171136; Homo sapiens. [Contig view]

KEGG hsa:117579; -.

Other

RZPD- ProtExp Clones: T3225

SOURCE RLN3; Homo sapiens.

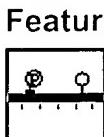
ProtoNet Q8WXF3.

UniRef View cluster of proteins with at least 50% / 90% / 100% identity.

Keywords

3D-structure; Cleavage on pair of basic residues; Direct protein sequencing; Hormone Signal.

Features



Feature table viewer



Feature aligner

| Key | From | To | Length | Description | FTId |
|---------|------|-----|--------|-------------------------------------|----------|
| SIGNAL | 1 | 25 | 25 | | |
| PEPTIDE | 26 | 52 | 27 | Relaxin-3 B chain (By similarity). | PRO_000C |
| PROPEP | 55 | 118 | 64 | Connecting peptide (By similarity). | PRO_000C |

| | | | | | |
|----------|-----|-----|----|------------------------------------------------------|----------|
| PEPTIDE | 119 | 142 | 24 | Relaxin-3 A chain (By similarity). | PRO_000C |
| DISULFID | 35 | 129 | | Interchain (between B and A chains) (By similarity). | |
| DISULFID | 47 | 142 | | Interchain (between B and A chains) (By similarity). | |
| DISULFID | 128 | 133 | | By similarity. | |
| STRAND | 29 | 32 | 4 | | |
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| TURN | 48 | 48 | 1 | | |
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| HELIX | 135 | 139 | 5 | | |
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Sequence information

Length: **142 AA** [This is the length of the unprocessed precursor]

Molecular weight: **15451 Da** [This is the MW of the unprocessed precursor]

CRC64: **23A3E095034B31E** is a checksum on the sequence

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| | | | | | |
| <u>70</u> | <u>80</u> | <u>90</u> | <u>100</u> | <u>110</u> | <u>120</u> |
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| | | | | | |
| <u>130</u> | <u>140</u> | | | | |
| LAGLSSSCCK | WGCSKSEISS | LC | | | |

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or at NCBI (USA)



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ProtScale, Compute pi/Mw, PeptideMass,
PeptideCutter, Dotlet (Java)

 ScanProsite, MotifScan



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SWISS-MODEL

 NPSA Sequence
analysis tools

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UniProtKB/Swiss-Prot: Q8WXF3 (REL3_HUMAN)

The section of the sequence Q8WXF3 (REL3_HUMAN) you have selected corresponds to:

PEPTIDE 26 52 Relaxin-3 B chain (By similarity).
 /FTId=PRO_0000016082.

In one-letter code:

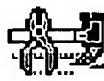
| | | | | | |
|----------------|------------|------------|------------|------------|----------|
| 1 | 11 | 21 | 31 | 41 | 51 |
| 1 MARYMLLLLL | AVWVLTGELW | PGAEARAAPY | GVRLCGREFI | RAVIFTCGGS | RWRRSDII |
| 61 EAMGDTFPDA | DADEDSLAGE | LDEAMGSSEW | LALTKSPQAF | YRGRPSWQGT | PGVLRGSI |
| 121 LAGLSSSCCK | WGCSKSEISS | LC | | | |

In three-letter code:

| | | | | | | | | | | | | | | | |
|---------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | |
| 1 Met | Ala | Arg | Tyr | Met | Leu | Leu | Leu | Leu | Ala | Val | Trp | Val | Leu | | |
| 16 Thr | Gly | Glu | Leu | Trp | Pro | Gly | Ala | Glu | Ala | Arg | Ala | Ala | Pro | Tyr | |
| 31 Gly | Val | Arg | Leu | Cys | Gly | Arg | Glu | Phe | Ile | Arg | Ala | Val | Ile | Phe | |
| 46 Thr | Cys | Gly | Gly | Ser | Arg | Trp | Arg | Arg | Ser | Asp | Ile | Leu | Ala | His | |
| 61 Glu | Ala | Met | Gly | Asp | Thr | Phe | Pro | Asp | Ala | Asp | Ala | Asp | Glu | Asp | |
| 76 Ser | Leu | Ala | Gly | Glu | Leu | Asp | Glu | Ala | Met | Gly | Ser | Ser | Glu | Trp | |
| 91 Leu | Ala | Leu | Thr | Lys | Ser | Pro | Gln | Ala | Phe | Tyr | Arg | Gly | Arg | Pro | |
| 106 Ser | Trp | Gln | Gly | Thr | Pro | Gly | Val | Leu | Arg | Gly | Ser | Arg | Asp | Val | |
| 121 Leu | Ala | Gly | Leu | Ser | Ser | Ser | Cys | Cys | Lys | Trp | Gly | Cys | Ser | Lys | |
| 136 Ser | Glu | Ile | Ser | Ser | Leu | Cys | | | | | | | | | |

Direct similarity search submission of this subsequence to

BLAST BLAST submission on
ExPASy/SIB
or at NCBI (USA)



Sequence analysis tools: ProtParam,
ProtScale, Compute pI/Mw, PeptideMass,
PeptideCutter, Dotlet (Java)



ScanProsite



Direct Submission to SWISS-MODEL

 NPSA Sequence
analysis tools

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SEQUENCE LISTING

<110> Del Borgo, Mark
Wade, John D.
Bathgate, Ross D.
Hughes, Richard A.
Howard Florey Institute of Physiology and Medicine
The University of Melbourne

<120> Relaxin Superfamily Peptide Analogues

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<140> US 10/561,304
<141> 2005-12-19

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<223> relaxin-2 b-chain

<400> 2
Asp Ser Trp Met Glu Glu Val Ile Lys Leu Cys Gly Arg Glu Leu Val
1 5 10 15

Arg Ala Gln Ile Ala Ile Cys Gly Met Ser Thr Trp Ser
20 25

<210> 3
<211> 27
<212> PRT
<213> Homo sapiens

<220>
<223> relaxin-3 b-chain

<400> 3
Arg Ala Ala Pro Tyr Gly Val Arg Leu Cys Gly Arg Glu Phe Ile Arg
1 5 10 15

Ala Val Ile Phe Thr Cys Gly Gly Ser Arg Trp
20 25

<210> 4
<211> 30
<212> PRT
<213> Homo sapiens

<220>
<223> insulin b-chain

<400> 4
Phe Val Asn Gln His Leu Cys Gly Ser His Leu Val Glu Ala Leu Tyr
1 5 10 15

Leu Val Cys Gly Glu Arg Gly Phe Phe Tyr Thr Pro Lys Thr
20 25 30

<210> 5
<211> 29
<212> PRT
<213> Homo sapiens

<220>
<223> insulin-like growth factor 1 (IGF-1) b-chain

<400> 5
Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe
1 5 10 15

Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr
20 25

<210> 6
<211> 31
<212> PRT
<213> Homo sapiens

<220>
<223> insulin-like growth factor 2 (IGF-2) b-chain

<400> 6
 Tyr Arg Pro Ser Glu Thr Leu Cys Gly Gly Glu Leu Val Asp Thr Leu
 1 5 10 15

Gln Phe Val Cys Gly Asp Arg Gly Phe Tyr Phe Ser Arg Pro Ala
 20 25 30

<210> 7
 <211> 31
 <212> PRT
 <213> Homo sapiens

<220>
 <223> insulin-like 3 (INSL3) b-chain

<400> 7
 Pro Thr Pro Glu Met Arg Glu Lys Leu Cys Gly His His Phe Val Arg
 1 5 10 15

Ala Leu Val Arg Val Cys Gly Gly Pro Arg Trp Ser Thr Glu Ala
 20 25 30

<210> 8
 <211> 33
 <212> PRT
 <213> Homo sapiens

<220>
 <223> insulin-like 4 (INSL4) b-chain

<400> 8
 Glu Ser Leu Ala Ala Glu Leu Arg Gly Cys Gly Pro Arg Phe Gly Lys
 1 5 10 15

His Leu Leu Ser Tyr Cys Pro Met Pro Glu Lys Thr Phe Thr Thr Thr
 20 25 30

Pro

<210> 9
 <211> 33
 <212> PRT
 <213> Homo sapiens

<220>
 <223> insulin-like 5 (INSL5) b-chain

<400> 9
 Val Arg Ser Lys Glu Ser Val Arg Leu Cys Gly Leu Glu Tyr Ile Arg
 1 5 10 15

Thr Val Ile Tyr Ile Cys Ala Ser Ser Arg Trp Arg Arg His Leu Glu
 20 25 30

Gly

<210> 10
 <211> 33
 <212> PRT
 <213> Homo sapiens

<220>
 <223> insulin-like 6 (INSL6) b-chain

<400> 10
 Ser Asp Ile Ser Ser Ala Arg Lys Leu Cys Gly Arg Tyr Leu Val Lys
 1 5 10 15

Glu Ile Glu Lys Leu Cys Gly His Ala Asn Trp Ser Gln Phe Arg Phe
 20 25 30

Glu

<210> 11
 <211> 25
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:cyclic relaxin
 b-chain mimetic (cRlx)

<220>
 <221> DISULFID
 <222> (2)..(24)

<400> 11
 Ser Cys Met Glu Glu Val Ile Lys Leu Ser Gly Arg Glu Leu Val Arg
 1 5 10 15

Ala Gln Ile Ala Ile Ser Gly Cys Ser
 20 25

<210> 12
 <211> 27
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence:insulin-like 3
 (INSL3)- b-chain peptide analogue 4, cyclic peptide
 cINSL3a

<220>
 <221> DISULFID
 <222> (3)..(25)

<400> 12
 Thr Pro Cys Met Arg Glu Lys Leu Ser Gly His His Phe Val Arg Ala
 1 5 10 15

Leu Val Arg Val Ser Gly Gly Pro Cys Trp Ser
 20 25

<210> 13
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:insulin-like 3
(INSL3) b-chain peptide analogue 5, cyclic peptide
cINSL3b

<220>
<221> DISULFID
<222> (3)..(25)

<400> 13
Thr Pro Cys Met Arg Glu Lys Leu Ser Gly Arg His Phe Val Arg Ala
1 5 10 15

Leu Val Arg Val Ser Gly Gly Pro Cys Trp Ser
20 25

<210> 14
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:insulin-like 3
(INSL3) b-chain peptide analogue 6

<400> 14
Thr Pro Cys Met Arg Glu Lys Leu Ser Gly Arg Glu Leu Val Arg Ala
1 5 10 15

Gln Val Ile Ala Ile Gly Gly Pro Cys Trp Ser
20 25

<210> 15
<211> 27
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence:insulin-like 3
(INSL3) b-chain peptide analogue 7

<400> 15
Thr Cys Glu Met Arg Glu Lys Leu Ser Gly His His Phe Val Arg Ala
1 5 10 15

Leu Val Arg Val Ser Gly Gly Cys Arg Trp Ser
20 25

<210> 16
<211> 24
<212> PRT
<213> Homo sapiens

<220>

<223> relaxin-1 a-chain

<400> 16

Arg Pro Tyr Val Ala Leu Phe Glu Lys Cys Cys Leu Ile Gly Cys Thr
1 5 10 15

Lys Arg Ser Leu Ala Lys Tyr Cys
20

<210> 17

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<223> relaxin-2 a-chain

<400> 17

Gln Leu Tyr Ser Ala Leu Ala Asn Lys Cys Cys His Val Gly Cys Thr
1 5 10 15

Lys Arg Ser Leu Ala Arg Phe Cys
20

<210> 18

<211> 24

<212> PRT

<213> Homo sapiens

<220>

<223> relaxin-3 a-chain

<400> 18

Asp Val Leu Ala Gly Leu Ser Ser Ser Cys Cys Lys Trp Gly Cys Ser
1 5 10 15

Lys Ser Glu Ile Ser Ser Leu Cys
20

<210> 19

<211> 26

<212> PRT

<213> Homo sapiens

<220>

<223> insulin a-chain

<400> 19

Ser Leu Gln Lys Arg Gly Ile Val Glu Gln Cys Cys Thr Ser Ile Cys
1 5 10 15

Ser Leu Tyr Gln Leu Glu Asn Tyr Cys Asn
20 25

<210> 20
<211> 25
<212> PRT
<213> Homo sapiens

<220>
<223> insulin-like growth factor 1 (IGF-1) a-chain

<400> 20
Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys Asp
1 5 10 15

Leu Arg Arg Leu Glu Met Tyr Cys Ala
20 25

<210> 21
<211> 25
<212> PRT
<213> Homo sapiens

<220>
<223> insulin-like growth factor 2 (IGF-2) a-chain

<400> 21
Arg Arg Ser Arg Gly Ile Val Glu Glu Cys Cys Phe Arg Ser Cys Asp
1 5 10 15

Leu Ala Leu Leu Glu Thr Leu Cys Ala
20 25

<210> 22
<211> 26
<212> PRT
<213> Homo sapiens

<220>
<223> insulin-like 3 (INSL3) a-chain (Leydig
insulin-like (Ley I-L)/relaxin like factor (RLF))

<400> 22
Ala Ala Ala Thr Asn Pro Ala Arg Tyr Cys Cys Leu Ser Gly Cys Thr
1 5 10 15

Gln Gln Asp Leu Leu Thr Leu Cys Pro Tyr
20 25

<210> 23
<211> 25
<212> PRT
<213> Homo sapiens

<220>
<223> insulin-like 4 (INSL4) a-chain (placentin/early
placenta insulin-like (EPIL))

<400> 23
Arg Ser Gly Arg His Arg Phe Asp Pro Phe Cys Cys Glu Val Ile Cys
1 5 10 15

Asp Asp Gly Thr Ser Val Lys Leu Cys
20 25

<210> 24
<211> 24
<212> PRT
<213> Homo sapiens

<220>
<223> insulin-like 5 (INSL5) a-chain

<400> 24
Met Ser Arg Gln Asp Leu Gln Thr Leu Cys Cys Thr Asp Gly Cys Ser
1 5 10 15

Met Thr Asp Leu Ser Ala Leu Cys
20

<210> 25
<211> 24
<212> PRT
<213> Homo sapiens

<220>
<223> insulin-like 6 (INSL6) a-chain

<400> 25
Arg Lys Arg Arg Gly Tyr Ser Glu Lys Cys Cys Leu Thr Gly Cys Thr
1 5 10 15

Lys Glu Glu Leu Ser Ile Ala Cys
20